BACH2 mediates negative selection and p53-dependent tumor suppression at the pre-B cell receptor checkpoint.

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Authors: Srividya Swaminathan, Chuanxin Huang, Huimin Geng, Zhengshan Chen, Richard Harvey, Huining Kang, Carina Ng, Bjorn Titz, Christian Hurtz, Mohammed Firas Sadiyah, Daniel Nowak, Gabriela B Thoennissen, Vikki Rand, Thomas G Graeber, H Phillip Koeffler, William L Carroll, Cheryl L Willman, Andrew G Hall, Kazuhiko Igarashi, Ari Melnick, Markus Muschen

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Public Summary:
The B cell-specific transcription factor BACH2 is required for affinity maturation of B cells. Here we show that Bach2-mediated activation of p53 is required for stringent elimination of pre-B cells that failed to productively rearrange immunoglobulin VH-DJH gene segments. After productive VH-DJH gene rearrangement, pre-B cell receptor signaling ends BACH2-mediated negative selection through B cell lymphoma 6 (BCL6)-mediated repression of p53. In patients with pre-B acute lymphoblastic leukemia, the BACH2-mediated checkpoint control is compromised by deletions, rare somatic mutations and loss of its upstream activator, PAX5. Low levels of BACH2 expression in these patients represent a strong independent predictor of poor clinical outcome. In this study, we demonstrate that Bach2(+/+) pre-B cells resist leukemic transformation by Myc through Bach2-dependent upregulation of p53 and do not initiate fatal leukemia in transplant-recipient mice. Chromatin immunoprecipitation sequencing and gene expression analyses carried out by us revealed that BACH2 competes with BCL6 for promoter binding and reverses BCL6-mediated repression of p53 and other cell cycle checkpoint-control genes. These findings identify BACH2 as a crucial mediator of negative selection at the pre-B cell receptor checkpoint and a safeguard against leukemogenesis.

Scientific Abstract:
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